REMARKS

I. Explanation of Amendments to the Specification and Claims

The application describes two human forms of the Asp2 protease ("Asp2(a)" and "Asp2(b)" splice variants) which differ from each other by the presence or absence of an internal stretch of about twenty-five amino acids. The Applicants believe that they have remained consistent and accurate in their presentation of the sequences for these splice variants, e.g. in Figures 2 and 3, but have identified inconsistencies in their applications relating to the names that are the subject of amendments set forth above.

More particularly, the present application refers to the longer splice variant as "Asp2(a)" and the shorter splice variant as "Asp2(b)." However, the Applicants have identified a few instances in the present application of inconsistencies, i.e., where "Asp2(a)" is used to refer to the shorter splice variant and "Asp2(b)" to the longer. The present amendment eliminates the inconsistencies.

The Brief Description of Figures 2 and 3 contained one such inconsistency, and the amendments at page 33 correct it. Figure 2 plainly depicts the "shorter" Asp2 sequence, and its description has been amended to recite "Asp2(b)" and to cross reference the shorter sequences in the Sequence Listing. The opposite amendment has been made for Figure 3, which plainly depicts the "longer" Asp2 sequence.[1] A similar amendment is made at page 49, where the application contains cross-references to Figures 2 and 3. The foregoing amendments ensure that the Specification consistently refers to the "longer" Asp2(a) polynucleotide and polypeptide as having the sequences set forth in SEQ ID NOS: 3 and 4, and the "shorter" Asp2(b) as having the sequences set forth in SEQ ID NOS: 5 and 6.

These amendments are supported by the application as filed because they simply make the terminology more consistent, and the inconsistencies and the manner in which they should be corrected would have been apparent to any reader of ordinary skill in the art. Moreover, the claims as amended do not use the "Asp2(a)" or "Asp2(b)" terminology. Thus, these amendments have no bearing on claim interpretation.

---

[1] In the description of Figure 3, the sentence pertaining to denoting the transmembrane domain has been deleted because the Figure lacks brackets and because the transmembrane domain is identified elsewhere in the specification.

The amendment at page 12 of the application addresses an informality identified by the Examiner in a related application and does not introduce new matter or change the meaning of the application in any way.

The sequences set out as SEQ ID NO: 3 and 4 in the substitute sequence listing, filed on April 30, 2001, are not identical to the sequences set out in Figure 3 as filed. Therefore, the second substitute sequence listing is submitted herewith to revise the sequences of SEQ ID NOS: 3 and 4 so that they are identical to the sequences shown in Figure 3 as filed. These amendments do not introduce new matter, but address an internal inconsistency. In addition, the sequence P2, P1, P1', P2' at page 15, line 7, was not previously assigned a sequence identification number. Although it may not be necessary, the second substitute sequence listing includes SEQ ID NO: 84 representing the sequence for P2, P1, P1', P2'. This sequence is defined in the specification at page 15, line 7-9, and therefore adds no new matter. The specification is amended at page 15 to include an appropriate cross-reference to P2, P1, P1', P2' as SEQ ID NO: 84.

In paragraph 1 of the restriction requirement the Patent Office observed that "claim 64 is missing" and indicated that "the claims have been renumbered and dependencies changed accordingly." However, the precise renumbering performed by the Examiner was unspecified. Moreover, the Applicants have observed that the original claim set also included two claims numbered "69".

For clarity, the Applicants request that any renumbering by the Patent Office be canceled. Referring to the original claims, the Applicants request that claims 65-69 (first instance) be renumbered as claims 64-68 as shown above, thereby providing a continuously numbered claim set from 1 to 77.

II. Restriction

Citing 35 U.S.C. § 121, the Examiner alleged that claims 1-77 were drawn to thirteen distinct inventions:

I. Claims 1-14, drawn to polynucleotides;

II. Claims 15-25, drawn to polypeptides;

III. Claims 26-35, 48-49 and 51-52, drawn to a method of screening with contacting hu-Asp1 or hu-Asp1 encoded by hybridizing nucleic acids;

IV. Claims 36 and 50, drawn to a method of screening further comprising treating Alzheimer's Disease;

V. Claims 37-46, drawn to a method of screening with transfected host cells;

VI. Claim 47, drawn to a method of screening with transfected host cells further comprising treating Alzheimer's Disease;

VII. Claims 53-67 and 70, drawn to a method for assaying hu-Asp1 α-secretase activity;

VIII. Claim 68, drawn to a method of assaying further comprising treatment of Alzheimer's Disease,

IX. Claim 69, drawn to a Asp1 protease substrate;

X. Claims 71-74, drawn to a composition that modulates APP processing;

XI. Claim 75, drawn to a composition that modulates APP processing;

XII. Claim 76, drawn to a composition that modulates APP processing; and

XIII. Claim 77, drawn to a composition that modulates APP processing.

Each of these thirteen groups was further restricted sixteen ways as discussed more fully below.

III. Election

The Applicants hereby elect Group VII, which includes Claims 53-67 and 70, drawn to a method of assaying hu-Asp1 α-secretase activity. Consistent with the requirement in paragraph 14 of the restriction requirement, the Applicants also hereby elect species 5 consisting of the APP substrate comprising. Consistent with the requirement set forth in paragraph 6 part A, the Applicants elect a polypeptide comprising at least residues 63-469 of SEQ ID NO: 2 (molecular embodiment no. 3). Consistent with the requirement set forth in paragraph 6, part B, the Applicants elect a determining step involving alpha secretase processing/activity (molecular embodiment no. 1). The Applicant make these elections with traverse.

IV. The Restriction Requirement Is Onerous And Unfair To The Applicants And The Public.

The application contains 77 claims which are all related in that they involve Asp1 polynucleotides, Asp1 polypeptides, methods of using the same to identify modulators of Asp1 activity, peptide substrates useful for such methods, and compositions comprising the modulators so identified. There are 77 total claims, ten of which are independent (claims 1, 13-15, 25, 26, 37, 48, 53, and 69).

Under "traditional" restriction practice, the Applicants might have expected the claims to be divided into as many as five groups, along the lines delineated above, with the possibility that process claims of appropriate scope might be rejoined with elected product claims. Until recently, the invention should have been completely protectable with, at most, a few divisional applications. In almost any other jurisdiction in the world, and under PCT practice, the Applicants would have an expectation that all of the claims would be examined simultaneously under a rational unity of invention standard.

However, in the present case, **the Examiner has seen fit to issue a 208-way restriction requirement** for the 77 pending claims. Specifically, the Examiner believes that there are thirteen traditional "Groups" (reproduced above) as a first tier of restriction (paragraph 4 of restriction requirement). This 13-way restriction is further MULTIPLIED by the instruction that "Furthermore, in addition to the election of one of the above XIII groups, further restriction is required . . . to delineate the molecular embodiment to which the claims will be restricted in accordance with the elected group." The Examiner then sets forth (A) four "molecular embodiments" and (B) four separate "determining steps" and states that "in order to be fully responsive applicant is required to elect a single Group from Groups I-XIII and a single [embodiment] from each of Groups A and B as set forth above." Thus, the Examiner considers that each of Groups I-XIII is properly further divisible sixteen ways.[2] The sixteen subdivisions of each of the 13 groups yields a total of 16 x 13 = 208 restriction groups for the 77 claims! The restriction is made still more onerous by the *further* inclusion of an election of species requirement for "method" claims spanning four of the Groups (i.e., Groups III, V, VII, and IX). (See Paragraph 14.)

---

[2] The sixteen combinations within each of the thirteen groups are A1-B1, A1-B2, A1-B3, A1-B4, A2-B1, A2-B2, A2-B3, A2-B4, A3-B1, A3-B2, A3-B3, A3-B4, A4-B1, A4-B2, A4-B3, AND A4-B4.

Under the Examiner's rationale, and ignoring the election of species requirement, the applicants would be required to file at least 208 patent applications at a cost of $153,920.00 in basic filing fees, $8320 in assignment recordation fees, $266,240.00 in issue fees, and $1,248,000 in maintenance fees over the life of the issued patents! In other words, the Applicants would be forced to pay in excess of $1.6 million in basic Patent Office fees alone, to fully protect the present invention. Even then, the Applicants still might not achieve full coverage for their invention due to the "election of species" requirement imposed by the Examiner affecting the sixty-four divisional applications that would be required to pursue Groups III, V, VII, and IX. (See paragraph 14 of restriction requirement.)

The unfairness of this position speaks for itself.

A 208-way restriction also works tremendous unfairness on the business public. The cost to competitors of analyzing more than 200 patents for infringement purposes is extremely burdensome, but would be a direct consequence of the Patent Office's new restriction policy. In this regard, the Patent Office's own manual warns, in capital letters, that "IT STILL REMAINS IMPORTANT FROM THE STANDPOINT OF THE PUBLIC INTEREST THAT NO REQUIREMENTS BE MADE WHICH MIGHT RESULT IN THE ISSUANCE OF TWO PATENTS FOR THE SAME INVENTION." (MPEP 803.01)

V. The Patent Office Has Failed To Set Forth A Prima Facie Basis For Restriction.

A. Failure to provide adequate reasons

According to Patent Office protocol, "Examiners must provide reasons and/or examples to support conclusions" in their restriction requirements.

It necessarily follows that an Examiner who believes that there are thirteen different "Groups" of inventions must justify this conclusion with reasons for dividing each group from the other twelve. Such analysis should entail seventy-eight pairwise analyses examining the relationship of Group I and II, Group I and III, Group II and III, and so on. In the present restriction requirement, no such analysis has been provided for the record for the Applicants to dispute. Instead, the Examiner has, in a few sentences, stated the *conclusion* that all of the product groupings are distinct from each other, all of the process groupings are distinct from each other, and that some of the products are distinct from the some of the processes. (See restriction requirement at paragraphs 9-11). A single, conclusory sentence in paragraph 8 is offered for further dividing the thirteen groups into 208 groups. In essence,

the Patent Office has attempted to transfer its burden of justifying a restriction to an Applicant's burden of proving that restriction is improper.

B. The Restriction to "Molecular Embodiments" is improper

In paragraphs 6-8 of the restriction requirement the Examiner subdivided each of the thirteen "Groups" into sixteen different "subgroups" (for a total of 208 restriction groups). The Examiner *admits* that "there are no provisions under the section for 'Relationship of Inventions' in MPEP 806.05 for inventive groups that are directed to different products." The fact that the MPEP does not have any provisions justifying the present restriction requirement is conclusive evidence that the restriction is improper:

> Where inventions as disclosed and claimed are both (A) species under a claimed genus and (B) related, then the question of restriction **must be determined by both** the practice applicable to election of species **and** the practice applicable to other types of restrictions such as those covered in MPEP §806.05 - §806.05(i). **If restriction is improper under either practice, it should not be required**.
>
> MPEP 806.04(b) (Emphasis added.)

In the present case, the Examiner admitted to finding no justification under section 806.05. This fact alone necessitates a conclusion that restriction should not be required.

As set forth below the MPEP's guidance in sections 806.03 and 806.04 involving genus-species issues also necessitates withdrawal of the rejection. The Patent Office's own rules *require* that "a reasonable number of species may still be claimed in one application . . . ." (See MPEP 806.04(a), citing 37 CFR 1.141.) The Examiner has ignored this rule and restricted the Applicants to single species.

1. The Applicants traverse the restriction of molecular embodiment in Group A.

In paragraph 8 of the Action, the Examiner required that the claims be restricted to a molecular embodiment directed to a particular Asp1 amino acid sequence. The Examiner stated that "restriction is deemed to be proper because the the products indicated ... constitute patently distinct inventions."

The Applicants do not dispute that full length amino acid sequence of SEQ ID NO:2 and fragments thereof can be distinct inventions. However, distinctness is not the only criteria for restricting inventions. In situations like the present, where the applicant has presented generic claims (see, e.g., claims 53 and 56). Claims should only be restricted to particular species when there is mutual exclusivity in the characteristics of the species. (See, e.g., MPEP 806.04(f)). The species being restricted by the Examiner all relate to SEQ ID NO: 2, mostly to overlapping portions thereof. The mutual exclusivity contemplated by the MPEP is lacking.

In such situations, the only restrictive practice envisioned by the MPEP is an "election of species" as described in MPEP 809. An election of species requirement differs from a restriction requirement in that, upon allowance of a generic claim, the applicant is entitled under the rules to consideration of additional species.

The issue of *serious* burden, another prerequisite to restriction, also has not been satisfied. The restriction requirement contains no indication that a search of a full length sequence and its fragments constitutes an undue burden on the Examiner. On the contrary, it is common practice within Group 1600 not to require separate searches for claims to fragments and the full length sequence. Claims such as the following: "A polypeptide comprising the amino acid sequence of SEQ ID NO: X and fragments thereof which exhibit a specific biological activity", are commonly searched without forcing the Applicant to choose between the amino acid sequence of SEQ ID NO: X and fragments of that sequence. The Applicants should not be forced to be restricted to claims reciting fragments and forced to pay additional filing fees solely because they have defined the fragments with additional specificity within the claim.

The Examiner states that the polypeptide fragments have unique structural and functional features that require a unique search of the prior art. The Applicants disagree that unique searches are necessary. The polypeptides listed in Group A comprise fragments of SEQ ID NO: 2 and therefore a search of the full length sequence should identify any sequences in the art which read on the fragments. The fragments may represent unique structural or functional domains of SEQ ID NO: 2, but the fragments can still be effectively searched together using SEQ ID NO:2 because they comprise fragments of SEQ ID NO: 2.

The Examiner also states that the polypeptide fragments are divergent sequences which are differentially able to bind and cleave. The Examiner has failed to

articulate any sound basis for this allegation. It is wrong to characterize these fragments as divergent sequences insofar as they all originate from a single full length sequence and have properties as a result of that sequence.

As discuss above, one search on the full length amino acid sequence will identify all possible sequences which read on the specific claimed fragments since the claim limitations relating to sequence involve the sequence of SEQ ID NO: 2. Moreover, since sequence searchers are relatively automated computer processes, no serious burden would exist if more than one sequence needed to be analyzed. The Applicants respectfully request that claims directed to the polypeptide fragments of SEQ ID NO: 2 be examined simultaneously (with any generic claims).

2. The Applicants traverse the restriction of molecular embodiment in Group B.

The Examiner required restricting the method claims to one molecular embodiment relating to a single determining step, but fails to provide adequate reasons for this restriction. In paragraph 8 of the action, the Examiner explains the reasoning why the restrictions of Group A and Group B are proper even though there is admittedly no provision requiring this restriction in the MPEP. As explained above, when the MPEP does not require restriction, it is because restriction is improper.

Also as explained above, the only requirement that the MPEP contemplates for claims of this nature is an election of species-type requirement. The subject matter is sufficiently related (compare claim 26 ("APP processing") and dependent claims 32 and 34 (α- and β-secretase processing)) with generic/linking claims that restriction is improper.

While α-secretase and β-sectease activities may be distinct, a unique search directed to a specific activity and its resulting product is not required. For example, a search for methods of identifying modulators of α-secretase activity will most likely identify methods which measure production of amyloid-α since that particular proteolytic activity only results in a limited number of products. In fact, it is fairly certain that the Examiner will look at all prior art teachings involving Asp1 activity, irrespective of which determining step is elected. Moreover, the field of study involving APP processing is such that a thorough search would be expected to identify literature related to the both α- and β-secretase processing.

In addition, the claims which measure production of amyloid-α or amyloid-β depend from the methods of measuring the appropriate secretase activity. These claims more particularly define the method and the Applicants should not be burdened with a restriction of these claims since they have narrow dependent claims which more particularly recite the metes and bounds of the invention. The Applicants respectfully request that all claims directed to methods of measuring α-secretase activity or β-secretase activity be examined simultaneously.

VI. Restriction Of The Claims Into 13 Groups Was Improper.

A. The Applicants traverse the restriction of claim Groups I and II.

The polypeptides of Group II are encoded by the polynucleotide sequence of Group I. It is probable that a search based on the polynucleotide sequences of Group I will involve the same prior art and identify similar art compared to a search based on the polypeptides of Group II. Moreover, existing search engines permit a searcher to search translations of known polynucleotide sequences in all reading frames automatically, permitting rapid comparisons of polynucleotide and polypeptide databases. Thus, it would not be a serious burden on the Examiner to do one search based on the claims in Groups I and II. Applicants respectfully request that the restriction requirement, in respect to Groups I and II, be withdrawn and these groups be examined simultaneously.

B. The Applicants traverse the restriction of Groups I and III and V.

The Group III and Group V methods of identifying agents that modulate the APP processing activity of hu-Asp1 comprise contacting APP with a polypeptide encoded by a hu-Asp1 polynucleotide of Group I. Just as it is proper to examine polynucleotides, vectors, and host cell claims, together in Group I, it is also proper to examine screening methods that use either the polynucleotides or the host cells together in a single group. The methods of both groups comprise the step of contacting hu-Asp1 and APP in the presence and absence of a test agent. The end result of the methods, identifying agents that modulate hu-Asp1 APP processing activity, is identical.

Claims of Group III are generic to claims of Group 5 since they do not stipulate how the hu-Asp is provided for in the method, whereas claims of Group V involve hu-Asp recombinantly expressed by a host cell. According to the MPEP, once a claim that is

determined to be generic is allowed, claims drawn to species in addition to the elected species will be allowable in view of the allowance of the generic claim. In order to expedite prosecution, the Applicants request that the claims of Group III and Group V be examined simultaneously since the relatedness of the methods do not impose a serious burden on the Examiner.

In addition, the Applicants point out that the claims of Group VII are also directed to methods that comprise a step of contacting hu-Asp1 polypeptide. This Group contains the independent method reciting methods using the hu-Asp1 polypeptide and dependent claims which require that the hu-Ap1 polypeptide be provided by in a cell transformed or transfected with a polynucleotide that encodes the hu-Asp1 polypeptide. The inclusion of dependent claims in Group VII is inconsistent with the Examiner's reasoning in restricting the related claims in Groups III and V.

Moreover, if the polynucleotides of Group I (product claims) are found novel and non-obvious under 35 U.S.C. §103(a), the Applicants may be entitled to rejoinder of claims to methods of using that product. *See* 1184 OG 86, (1996). The Applicants hereby request that, if the product claims of Group I are allowed, the Patent Office rejoin the method claims of Groups III and V. To facilitate efficient examination, the Applicants request that the claims of Groups I , III and V be examined simultaneously. The relatedness of the claims of Groups III and V to the claims of Group I suggest that there will be no serious burden involved. Applicants respectfully request that the restriction requirement, in respect to Groups I , III, and V be withdrawn and these groups be examined simultaneously.

C. The Applicants traverse the restriction of Group VII from Groups II or Groups III and V.

Groups II and VII are related as product and method of use; as explained above in Part B, the Applicants may be entitled to rejoinder in this circumstance anyway, and there would be no serious burden in examining the products and methods together at the same time.

Groups III, V, and VII are all related insofar as they involve screening assays investigating Asp1 proteolytic activity. Even though Groups III and V define the polypeptide with reference to nucleic acids or recombinant cells, the fact remains that the claims all involve assays of proteolytic activity. A thorough search involving any individual group will require an examination of the Asp1 art and/or protease assay art (if any) relevant to the other

groups. Accordingly, the claims are related and there would be no serious burden in examining them together.

D. The Applicants traverse the restriction of Groups III and IV.

The claims of both Group III and IV are directed to methods of identifying agents that modulate hu-Asp1 APP processing activity. The claims of Group IV comprise the additional step of treating Alzheimer's Disease with the agent identified. This interrelatedness of Groups III and IV is substantiated by the fact that the claims of Group IV depends from claims of Group III. The Applicants request that the claims of Group III and Group IV be examined simultaneously. The small number of claims within Group IV and their relatedness to Group III suggests that there will be no serious burden involved. In addition, it is a well known in the art that APP processing activity is related to the formation of amyloid plaques associated with Alzheimer's Disease. Therefore a search based on methods with the single additional step relating to Alzheimer's Disease does not impose a serious burden on the Examiner. Applicants respectfully request that the restriction requirement, in respect to Groups III and IV, be withdrawn and these groups be examined simultaneously.

E. The Applicants traverse the restriction of claim Group V and VI.

The claims of both Groups V and VI are directed to methods of identifying agents that modulate hu-Asp1 APP processing activity. The claims of Group VI comprise the additional step of treating Alzheimer's Disease with the identified agent. This interrelatedness of the claims of Groups V and VI is substantiated by the fact that the claim of Group VI depends from a claim of Group V. The Applicants request that the claims of Group V and Group VI be examined simultaneously. The single claim within Group VI and its relatedness to Group V suggests that there will be no serious burden involved. In addition, it is a well known in the art that APP processing activity is related to the formation of amyloid plaques associated with Alzheimer's Disease. Therefore a search based on methods with the single additional step relating to Alzheimer's Disease does not impose a serious burden on the Examiner. Applicants respectfully request that the restriction requirement, in respect to Groups V and VI, be withdrawn and these groups be examined simultaneously.

F. The Applicants traverse the restriction of claim Group VII and VIII.

The claims of both Group VII and VIII are directed to methods of assaying hu-Asp1 α-secretase activity. The methods in claims of Group VIII comprise the additional step of treating Alzheimer's Disease. This interrelatedness of Groups VII and VIII is substantiated by the fact that the claim of Group VIII depends from a claim of Group VII. The Applicants request that the claims of Group VII and Group VIII be examined simultaneously. The single claim within Group VIII and its relatedness to Group VII suggests that there will be no serious burden involved. In addition, it is a well known in the art that APP processing activity is related to the formation of amyloid plaques associated with Alzheimer's Disease. Therefore a search based on methods with the single additional step relating to Alzheimer's Disease does not impose a serious burden on the Examiner. Applicants respectfully request that the restriction requirement, in respect to Groups VII and VIII, be withdrawn and these groups be examined simultaneously.

G. Applicants traverse the restriction of claim Groups IX and X.

If the peptide substrates of Group X (product claims) are found novel and non-obvious under 35 U.S.C. §103(a), the Applicants may be entitled to rejoinder of claims to methods of using that product. *See* 1184 OG 86, (1996). The Applicants hereby request that, if the product claims of Group IX are allowed, the Patent Office rejoin the method claims of Group X. To facilitate efficient examination, the Applicants request that the claims of Groups IX and X be examined simultaneously. Applicants respectfully request that the restriction requirement, in respect to Groups IX and X be withdrawn and these groups be examined simultaneously.

H. Applicants traverse the restriction of claim Groups XI, XII and XIII.

The claims of Group XI and XIII are directed to compositions comprising an agent that modulates APP processing activity as identified by the methods of Group III. These composition are identified by methods that contact APP and hu-Asp1 in the presence and absence of a test agent and determine APP processing activity. Claim 26, from which claim 75 (Group XI) depends, recites contacting with hu-Asp1 regardless of the source, whereas claim 48, from which claim 77 (Group XIII) depends, requires that the hu-Asp1 used in the method be encoded by a nucleic acid molecule that hybridizes under stringent conditions to the polynucleotide sequence of SEQ ID NO: 1. The Examiner did not require an election between claim 26 and claim 48, therefore an election between Groups XI and XIII is inconsistent.

Furthermore, the claim of Group XII is directed to a composition comprising an agent that modulates APP processing activity as identified by the methods of Group V. These compositions are also identified by methods that contact APP and hu-Asp1 in the presence and absence of a test agent and determine APP processing activity. Claim 37, from which claim 76 (Group XII) depends, requires that hu-Asp1 used in the method be expressed by a host cell, and APP contact that host cell. As described in section F of this response, the applicants dispute the restriction between Groups III and V. The compositions of Group XII are identified by related methods to those in Group XI and XIII, therefore there is no serious burden in examining these groups simultaneously. Applicants respectfully request that the restriction requirement, in respect to Groups XI, XII and XIII be withdrawn and these groups be examined simultaneously.

VII. The Allegations Relating To Markush Groups Were Improper And Do Not Support Restriction.

In paragraph 3 of the restriction requirement the Patent Office alleged that "applicants have presented instant claims in improper Markush format" and cited MPEP §803.02. The Patent Office failed to identify any improper claims with particularity. The Applicants respectfully traverse.

A. The Patent Office has failed to meet its duty of providing reasons or examples.

The Patent Office instructs that "Examiners must provide reasons and/or examples to support conclusions . . . ." (MPEP 803) The present allegations fail to satisfy this requirement. The Examiner made boilerplate allegations that "the claims define multiple structurally distinct compounds capable of different use, with different modes of operation, different function and different effects." However, these allegation were not supported with the specific identification of any defective claim, or any example of compounds with these alleged differences, or any statement of what the differences were. The Examiner alleged that a reference against one component or method would not be a reference against another, but did not give an example supporting this allegation either. For these reasons alone, the allegations should be withdrawn.

B. None of the claims contain improper Markush Groups.

The MPEP instructs that a Markush group is proper so long as the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship. (See, e.g., MPEP 2173.05(h).) Where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and not on whether the Markush expression per se has a "community of properties."

Claims 1 and 15 are directed to Asp1 polynucleotides which encode proteolytically active portions of a human Asp1 protein. Although Markush-type language is used to define characteristics that are *absent* from the polynucleotides of these claims, it is clear that all of the members of the claimed genera possess common structural (human Asp1) and functional (encoding proteolytically active protein) properties.

Claims 28 and 45 each recite Markush groups of polynucleotides that encode Asp1 polypeptides. The members of the group share common structure (e.g., encoding all or a portion of SEQ ID NO: 2 or sufficiently similar in structure so has to hybridize under stringent conditions) and common function (Asp1 APP processing activity). It is well accepted that biological function of molecules is attributable to the structure of those molecules, and it is well accepted to define a genus of polynucleotides using hybridization condtions. Thus, the Markush groups of these claims is proper.

Claim 62 recites a two-member group which comprise a common structural (LVFFAED) and functional (cleavable by Asp1) properties.

Claim 65 recites a Markush group of three well-recognized classes of labels that molecular biologists attach to biomolecules. There was no objection to the Markush group of labels.

Thus, all of the claims which recite Markush groups are in proper form, and the objection alleging otherwise should be withdrawn.

C. Restriction of the Markush claims is improper.

The restriction requirement includes an allegation that, irrespective of which group is elected, further restriction is required "to delineate the molecular embodiment to which the claims will be restricted." Insofar as this allegation relates to the Markush claims, it is improper. The MPEP sections cited by the Examiner provide a two-part test for assessing the propriety of restricting Markush Groups:

> Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), **it is improper for the Office to refuse** to examine that which applicants regard as their invention, **unless the subject matter in a claim lacks unity of invention**. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, **unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility**.

See MPEP §803.02. (Emphasis added.)

The claims in the present application satisfy these criteria. The polynucleotides of claims 1 and 15 encode proteases with a common proteolytic activity (a common utility) which is attributable to common structural features recited in the claims (i.e., the encoded amino acid sequence).

Claims 28 and 45 recite a Markush group of nucleotide sequences. All of the sequences share a common structural feature of encoding an Asp1 protein (see parent claims 27 and 37) which is essential to a common utility involving use of an active protease in the claimed screening assays.

The Markush group of peptides in claim 62 share a common primary amino acid sequence core which is essential for its utility as a cleavage substrate for Asp1.

For these reasons, there is no valid basis for restricting any of the Markush claims.

CONCLUSION

In light of the forgoing remarks, the Applicants request withdrawal of the 208-way restriction requirement entirely or rewriting to reasonable number (2 to 5) of restriction groups.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

By: 

David A. Gass.
Reg. No. 38,153

June 3, 2002

APPENDIX A

MARKED UP VERSION OF AMENDMENTS TO SPECIFICATION AND CLAIMS

IN THE SPECIFICATION

Amendment of paragraph beginning at page 12, line 9:

--Several species are particularly contemplated. For example, the invention provides a nucleic acid [and] molecule wherein said Hu-Asp polypeptide is Hu-Asp1, and said polynucleotide molecule of [1(a)] (a) comprises the nucleotide sequence of SEQ ID NO.1; and a nucleic acid molecule wherein said Hu-Asp polypeptide is Hu-Asp2(a), and said polynucleotide molecule of [1(a)] (a) comprises the nucleotide sequence of SEQ ID NO. [4] 3; and a nucleic acid molecule wherein said Hu-Asp polypeptide is Hu-Asp2(b), and said polynucleotide molecule of [1(a)] (a) comprises the nucleotide sequence of SEQ ID NO. 5. In addition to the foregoing, the invention provides an isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent conditions to a polynucleotide having the nucleotide sequence in (a) or (b) as described above. --

Amendment of paragraph beginning at page 15 line 1:

--In one variation, the cells are collected and the critical peptide is the APP C-terminal peptide created as a result of the β secretase cleavage. In another variation, the supernatant is collected and the critical peptide is soluble APP, where the soluble APP has a C-terminus created by β secretase cleavage. In preferred embodiments, the cells contain any of the nucleic acids or polypeptides described above and the cells are shown to cleave the β secretase site of any peptide having the following peptide structure, P2, P1, P1', P2' (SEQ ID NO: 72, where P2 is K or N, where P1 is M or L, where P1' is D, where P2' is A. [The method of claim 111 where] In one embodiment P2 is K and P1 is M[. The method of claim 112 where] and in another embodiment P2 is N and P1 is L. --

Amendment of paragraph beginning at page 33 line 17:

--Figure 2: Figure 2 shows the nucleotide (SEQ ID NO: [3] 5) and predicted amino acid sequence (SEQ ID NO: [4] 6) of human [Asp2(a)] Asp2(b). --

Amendment of paragraph beginning at page 24 line 1:

--Figure 3: Figure 3 shows the nucleotide (SEQ ID NO: [5] 3) and predicted amino acid sequence (SEQ ID NO: [6] 4) of human [Asp2(b)] Asp2(a). [The predicted transmembrane domain of Hu-Asp2(b) is enclosed in brackets.] --

Amendment of paragraph beginning at page 59 line 13:

-- Several interesting features are present in the primary amino acid sequence of Hu-Asp2(a) (Figure [2] 3 and SEQ ID No. 4) and Hu-Asp-2(b) (Figure [3] 2, SEQ ID No. 6). Both sequences contain a signal peptide (residues 1-21 in SEQ ID No. 4 and SEQ ID No. 6), a pro-segment, and a catalytic domain containing two copies of the aspartyl protease active site motif (DTG/DSG). The spacing between the first and second active site motifs is variable due to the 25 amino acid residue deletion in Hu-Asp-2(b) and consists of 168-*versus*-194 amino acid residues, for Hu-Asp2(b) and Hu-Asp-2(a), respectively. More interestingly, both sequences contains a predicted transmembrane domain (residues 455-477 in SEQ ID No.4 and 430-452 in SEQ ID No. 6) near their C-termini which indicates that the protease is anchored in the membrane. This feature is not found in any other aspartyl protease except Hu-Asp1. --

IN THE CLAIMS

[65.] 64. (Amended) A method of claim 53, wherein the detectable label is selected from the group consisting of radioactive labels, enzymatic labels and flourescent labels.

[66.] 65. (Amended) A method of claim 53, wherein the APP substrate comprises a human APP isoform and further comprises a carboxy-terminal di-lysine.

[67.] 66. (Amended) A method of claim 53, wherein the APP substrate comprises a human APP isoform and the determining step comprises measuring the production of amyloid alpha peptide (sAPPα).

[68.] 67. (Amended) A method of claim [66] 53, wherein the method further comprises steps of:

(c) determining the level of hu-Asp1 α-secretase activity in the presence and absence of a modulator of hu-Asp1 α-secretase activity; and

(d) comparing the hu-Asp1 α-secretase activity in the presence and absence of the modulator, wherein modulators that increase hu-Asp1 α-secretase activity are identified as candidate Alzheimer's disease therapeutics.

[69.] 68 (Amended) A method of claim 67, wherein the method further comprises a step of treating Alzheimer's Disease with said candidate Alzheimer's disease therapeutic.

70. (amended) The substrate of claim [68] 69, wherein the substrate comprises a detectable label.